American Journal of Pharmacy

AND THE SCIENCES
SUPPORTING PUBLIC HEALTH

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of Pharmacy and Science

(See Dr. Griffith's Article on
Public Relations With Science)

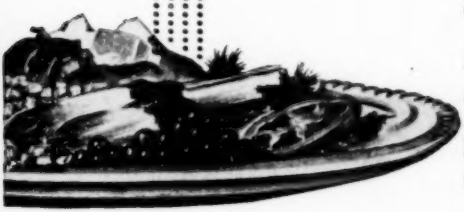
Since 1825 *January 1952*

American Journal of Pharmacy

Published monthly by the Philadelphia College of Pharmacy and Science
43d Street, Kingsessing and Woodland Avenues, Philadelphia 4, Pa.

Annual Subscription, $4.00 — Foreign Postage, 25 Cents Extra
Single Numbers, 40 Cents — Back Numbers, 50 Cents

Entered as Second-Class Matter March 27, 1937, at the Post Office at Philadelphia, Pa.
Under Act of March 3, 1879



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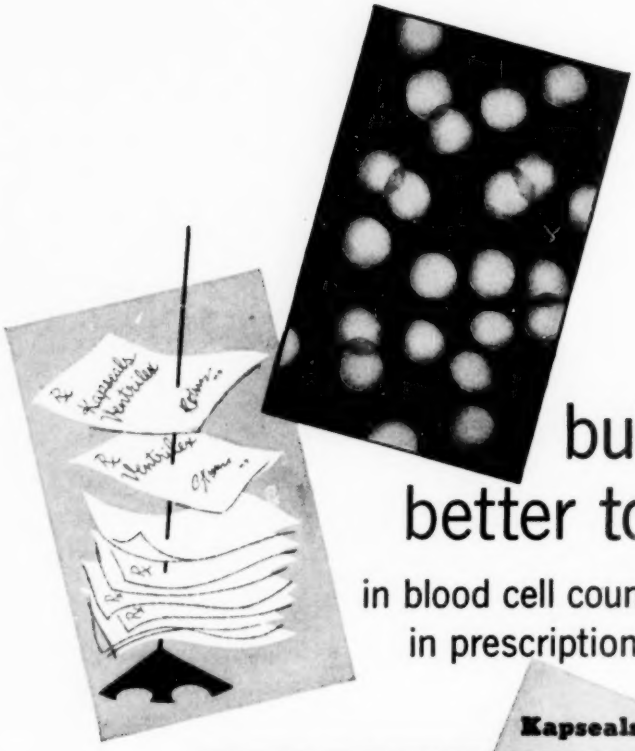

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AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

Vol. 124 JANUARY 1952 No. 1

CONTENTS

E D I T O R I A L

NARCOTICS CONTROL—A WORLD PROBLEM

EVERY civilized country is aware of the problem of narcotic drug addiction, although efforts toward the control of this practice vary greatly in intensity and direction.

In our own country illicit traffic in narcotics has become a part of the operations of the underworld, immense in its proportions but carefully screened so that public apathy will not be too much disturbed. Some few reflections on the origin of this evil and how it is perpetuated seem in order.

The development of a well-organized underworld in the United States was the direct result of that famous but unsuccessful experiment, Prohibition. This attempt to legislate morality lacked that preponderance of public support necessary for any law to succeed in practice. Millions of Americans laughed at the ingenuity with which the law was violated and the successful "bootleggers" and "rum runners" became public figures admired by the millions who chose to purchase their wares.

For the first time in the history of the United States there was widespread disrespect for a law at the highest level, namely, an amendment to the Constitution. The damage done to public morals by this experience will never be fully assessed for it led to today's callous attitude toward all laws and the weakening of our moral fiber as a nation.

With the repeal of prohibition those who had been trafficking in alcoholic beverages found themselves rapidly separated from their lucrative business. It was only natural that they would seek other areas for their well-organized groups to operate outside the law. We know, today, the answer: gambling, prostitution and narcotics. These collectively are a multi-billion dollar industry. So powerful have these groups become that it has become a national scandal investigated by special Senate and House Committees. These in themselves can do little except punish a few individuals for either perjury or contempt unless they succeed in arousing public opinion and changing public attitude.

Of all the underworld activities the public gives the least moral support to illicit narcotic distribution and the police and others concerned in suppressing this evil have public opinion behind them. There are certain factors, however, which make the narcotic problem

an extremely difficult one. Space will not permit a full discussion of these factors and we shall describe only a few.

One factor of great significance is the world production of narcotic drugs which greatly exceeds the world's legitimate medicinal needs. Figures recently published by the United Nations are almost unbelievable in their implication. In Italy, for example, there was at the end of 1950 a reported loss of 164 Kg. of diacetylmorphine, this presumably now being in illicit channels. The Central Opium Board also reported that in Iran alone the figure for present stocks of opium together with those of previous stocks, production and exports show that 360 tons have disappeared! If this contained 10 per cent morphine it would represent 72,000 lbs. of morphine which equals 2 billion one-quarter grain doses—this from only one source of opium production!

With such tremendous quantities available for illicit trade, with American dollars needed abroad and with our own underworld waiting and ready to pay the price it is not surprising that much of this illicit material finds it way here.

Nothing, unless it be diamonds, occupies less space for dollar value represented, and considerable quantities of narcotics undoubtedly get into the country, since our seacoasts are thousands of miles long as are our international boundaries. With this veritable flood descending on us it is no wonder that much gets by Treasury Department operatives, Customs Officials and the police.

The encouragement of addiction is practiced by the underworld since once an addict there is no recourse except to buy illicit drugs at whatever price is demanded. In England an addict may be maintained legally by a practicing physician and thus he is not forced to patronize the underworld. Quite possibly this explains the much smaller extent of addiction in England for this reduces the incentive to encourage addiction as a means of increasing one's customers.

The unending battle continues with law enforcement officials never quite able to cope with the situation. Well-organized gangs continue to receive illicit drugs from abroad, distribute them and even promote addiction among our youth. The logical answer seems a world-wide effort to control opium production at that level compatible with legitimate needs. Such a program would not seem impossible nor inconsistent with the United Nations aims and ideals. Without such correction at the source it seems that most of our efforts domestically will continue to be of only limited success and narcotic addiction will continue to cause untold human misery and depravity.

L. F. Tice

OPERATION KNOWLEDGE—
PUBLIC RELATIONS WITH SCIENCE *

By Ivor Griffith,** Ph.M., Sc.D., F.R.S.A.

THE text, which I am expected to enlarge into context and, I trust, into a wearable (durable) texture too, has so many facets of interpretation that I find it difficult to know just which area into which to excursion this afternoon.

Benjamin Franklin, it is, who stands as the first outstanding American exponent of popular science. He did it, not as so many people believe, by "flying a kite," but by his deliberate cultivation of public interest of the cause of science. This great Philadelphian and great American used as his medium of speech an intelligent, intelligible, everyday language.

Since his day there has been a definite plan and performance to interest people in the findings of science, although even today we find a breed of scientists who fail to see else than crass attempts at vulgar show in the efforts of those who try to bring the thoughts of true science into a language that fitteth all understanding. They do not realize that it is better that the secret press of science come from beyond its curtain and give its candid story to the public mind and that scientists shall no longer write only in a language for scientists, which so far as the average person is concerned might just as well be Macedonian. They do not seem to appreciate that the education of the masses even superficially in the diversified fields of science lessens the chance of the quack and the crook.

Thank goodness, however, that, on the other hand, there are well informed persons in the field of science who have laid aside the high brow high hat and are now on speaking terms with the laity.

The late beloved Edwin Emery Slosson, whose splendid books, notably *Creative Chemistry*, and whose fine plan which initiated the now famous "Science Service" and "Science News Letter of Washington" was more responsible than anyone in alerting science to the public and the public to science.

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* Presented at the December, 1951, Meeting of the American Association for the Advancement of Science.

** President of the Philadelphia College of Pharmacy and Science.

Since his day, through the medium of the press, the radio and television, the average citizen is more science conscious than ever in our history and all of this is for good.

May I, accordingly, challenge our thinking for the next few minutes under the following captions:

a. Science in Character Building

b. The Benefit of a Science Conscious Public

Science in Character Building

I believe that I am not wrong in interpreting the caption of my address when I regard the very fundamental truth that a knowledge of the sciences helps to build *character* in young people.

Science is an ever solvent search for truth, and it operates with the unremitting faith that the truth is worth searching for whether it hurts or whether it heals.

Said Pilate, that unwitting instrument of the greatest plan ever conceived for the redemption of the sub-angelic sons of Adam, "What is Truth?" and Adam himself, we must remember, was something of a researcher, hence the apple episode and the forthwith transfer of the primal pair to Eden suburbs, leaving us, their children, a legacy of sin and sweat.

Euripedes said, "Time will discover everything to posterity. It is a babbler and speaks even when no question is put." Thus we must always remember that what is now called true is only currently true. Science is never the whole truth but rather the continued colation of the eternally yielding marc of universe with the menstrua of knowledge, industry and honesty. As such, science has been and is, one of the most accelerating catalysts in man's evolution, although it could be that it shall bring his destruction too.

Science merely reflects the social forces which surround it. When there is peace, science is constructive; where there is war, science is perverted to destructive industry, and there is no question but that the advances of the last war and since, notably atomic fission and atomic fusion, have brought humanity to the doorstep of doom and we are faced with the urgent question,—"Can education and tolerance and understanding and creative intelligence run fast enough to keep us abreast with our mounting capacity to destroy?"

There are substantial proofs as well as reasons why the continuing search for truth involved in science, is necessarily and funda-

mentally a developer of character in the individual." Brusquely, let me ask you to search your own minds for a character cross-section of scientists and then compare it with the character cross-section of a representative group of business men, bankers, artisans, artists, musicians, and others. Is it not a fact that the fine attributes of fidelity of purpose, of a respect for the truth, of a devotion to human welfare, and service above self, are more manifest in a group of true scientists than in any other group of practitioners.

True science should be the true democracy and I am inclined to believe that if we could replace the financiers, the politicians and the war mongers of the earth by a council of true scientists, the government of the world would take a turn for the better and it might be on earth as it is in Heaven.

In America, great strides have been achieved in the training of scientists, but we have sadly missed one important step, namely, to arrange things so that every child in this country, while the mind is plastic and adaptable might be taught something of the fundamentals of science. In our secondary training we have gone haywire over vocational training and the social sciences and we have neglected those phases of science which might truly be considered the humanities.

Mind you, I am not questioning the validity and the value of teaching, in their proper place, the social sciences and vocational issues, but they should be corner-stoned with the basic fundamentals of those sciences which explain man's position in the universe and as Pope put it "the greatest study of mankind is man."

Here is where we have our chance to teach young Americans to be able to judge the facts and the progress of science when they have become mature enough to use such an understanding of the search for truth.

What did Thomas Huxley mean when he referred "to a mind stored with the knowledge of the great and fundamental truths of nature and the laws of her operation," if he did not mean that a truly educated man, whether he be a preacher or a priest, a lawyer or a stock broker, a professor of English or a chemist or any such practitioner had to be aware of the fundamentals of zoology and biology, of physics, of chemistry, of mathematics and the like?

The fine tomorrow of this great democracy can only come to pass if every current generation insists on training its youth in such wise that the following generation will inevitably be an improvement over the generation which preceded it.

Let us just think over some current capitalization for profit of the ignorance of many in our society. I marvel how blatant advertisers of this day and age have the temerity to insult the intelligence of the conscious public with claims made for their products. Certainly in a well educated society the foolishnesses which are spread on the minutes of the radio and television would never be permitted.

It is a queer commentary on the credulity of the public that much of its health education comes not from legitimate, expert, qualified sources, but from coiners of catch phrases and sounders of sonorous phrases who conduct their subsidized course of lectures in the advertising columns of our allegedly responsible and respectable press and now in the wide open university of air-borne advertising. And what a college of liberal arts this is, and millions of morons have matriculated into its lackadaisical course. Tuition terms are terse and trivial and anyone may enter and everyone graduate. The major faculty of this great institution of earning and learning seems to be mostly the happy trick of taking a lie, twisting it deftly to make it seem true, then salving it with a little sense, greasing it with sound and sending it along to its destiny.

Claims made, for instance, for cigarettes on the radio, on the television screen, and in the press are so truly ridiculous, and yet tens of thousands for lack of better understanding believe, them. "A treat instead of a treatment," "The long pull to filter the smoke," "Not a cough in a carload," and one brand lately proclaims that more doctors smoke them than any other cigarette, as if that was scientific evidence of their wholesomeness.

Then of dental advertising and other health education whose curriculum is unlimited. Under this magic ministry yeast, common kitchen yeast, is no longer a cook's accomplice, breeder of gas in bread, but rather a full fledged medical agent with credentials from funny faced foreign geheimrats and from physicians in waiting to queens and tenspots. Yeast has quit the kitchen for the medicine cabinet. Of which, if we believe its sellers it need be the only tenant. In the past decade or so more diseases have been discovered and named by writers of advertising hooey than by all the white-robed workers in the scientific field. Just recently, elsewhere and plenty-where is spread the lieing message of a new star in the hokum firmament, a cureall that challenges the medical dictionary to name any disease which it will fail to remedy, and people who will run and read, read and run to the nearest shop to buy a bottle.

Girth control for Fisher bodies is seemingly more on the roster than birth control and varieties of vitamins lastly more stressed than sensible food stuff. Crank case oil, frightened with vitriol to a palatable paleness, is paraded under sonorous synonyms and recommended as the suavest and smoothest persuader of a pretty peristalsis. Red ray lamps that emit no better emanation than a red hot plate of pepper pot are pictured as health granting gifts of God. Indeed, we could continue *ad infinitum, ad nausem,* with such examples of the advertising universities experts, but sufficient has been presented to prove, I believe, that people trained in science while young will not be prey for nonsense of this kind when they become real consumers. Thus, I believe that I have stressed a very important fact, namely, that by training all young Americans in the sciences we shall effectuate a real step toward a more intelligent and a less gullible democracy.

I have not paid my compliments to newspapers and periodicals which in their columns have indicated a high sense of ethics and moral obligation to the public in connection with their interpretation of science, its findings and its fineness. We have many publications here in Philadelphia that reflect honor on themselves and on their readers because of the consummate care which they take in presenting the news and the facts of science. That an occasional error creeps in is understood and in all likelihood is lost on a great majority, although I should like to see a scientific editor on every large newspaper in the country.

One of the participants in this panel, Dr. Waldemar Kaempffert, is a splendid example of one who has made an earnest contribution to reporting science in the public press accurately and understandably. And Mr. Watson Davis has done an equally far-reaching job, following so effectively in the steps of Dr. Slosson.

The same kind of scientific supervision should be given to television broadcast pictures and on the movie screen, for these today are tremendous sources of information and a report of what goes on in science. A number of such programs are already being shown, and I am sure, based upon what I have seen, that they are all done with the characteristic accuracy of science itself.

The Value of a Science Conscious Public

The field of medicine has distinguished itself in earning confidence and the esteem of the public. Generally speaking, man's health

is his chiefest concern and accordingly, the custodians of this fact, the medical group, has evidenced as unusual appreciation and respect. So much so, indeed, that John O. Public thinks more of his physician than he does of his spiritual adviser or his barber.

The popular health magazine "Hygeia" underwritten profitably, of course, by the A. M. A., has been extremely effective in distributing favorable yet accurate reports of the advances in medicine. I am now referring, of course, to its news and article content, exclusive of advertising. The medical almanac of many a back woods farmer is today the "Readers Digest", and it is believed that most of the material published there and in similar periodicals is trustworthy and respectable. No meager contribution has been made to health education in America by these sources. By this interpretation of the service of medicine, men with means have been encouraged to make tremendous contributions in money toward research and it is said that in America today we are spending nearly a quarter of a billion dollars a year on research in cancer, that great disease of civilization. Indeed, we are coming closer all of the time toward the sensible and economical spending of this money in cancer research so that ultimately we may have a concerted program, avoiding duplication of experiments. I make this statement because all over the world there are thousands of dissociated projects researching into the various aspects of cancer. Today much too little cooperation is executed between these projects. Some are completely chemical; some, believe it or not, are metaphysical. Doctors, chemists, biologists, bacteriologists, pathologists, physicists, mathematicians, statisticians, homeopaths, allopaths and several other paths and a few detours are all hodge podging this physiological crusade with a minimum of coordination and cooperation. Fine philanthropists and some others angry at the income tax give freely of their money to these unrelated researches, yet let me remind you that the government of the United States through organization and with plenty of money has managed to solve atomic fission and atomic fusion, although solution of the problem that produced the deadly and dastardly atomic bomb required the work of about one hundred and twenty-five thousand people and an expenditure of between two and three billions of dollars with months and months of weary researching brought the ultimate result. Why? "concentration and coordination" made this grave and epoch-making discovery possible, yet I submit to you that this most deadly of all human enemies, cancer, could be wiped from the face of the earth if the same

sort of intelligent, coordinated insistence were exercised in this direction as was used in the case of the atomic bomb.

The medical profession has also been able to enlist the interest of well motivated people in conducting campaigns of education and financial assistance in many other areas of public health or lack of it, for instance, the American Heart Association, the Arthritis and Rheumatism Foundation, the Tuberculosis Group, the American Social Hygiene Association, the Multiple Sclerosis Group, the American Cancer Society and many, many others, most of them operated by lay persons guided by medical scientists, all joining in a tremendous work to educate the public and to interest them in helping those less fortunate.

Actually, this is one area which stands out as having brought to public consciousness information to stimulate them toward self-preservation and toward making life a little more comfortable for the afflicted. This is one of the reasons why we have had such achievement in the field of public health in America in the last half century.

The life span of a child born now has an expectancy of practically a quarter of a century beyond the life span of a child born fifty years ago. Incidentally, I believe that this very gift of twenty-five years to life imposes upon society still greater need for looking toward the welfare of the aged and also to teaching people from their early years in the field of science and elsewhere so that they may know how to spend the new gift of a longer life wisely. I sincerely hope one of these days to find that some forward looking university will establish a course entitled something like "Economics of Gerontology" or "Preparation for Retirement," so that the coin of leisure may be spent with profit and wisely.

I have not attempted to burden the presentation with the growing appreciation of science by industrialists. This is common-place knowledge, but I do believe that too little has been done in a clinical, practical way so that industry may make its spiritual and material contributions to science so that we shall not only have an adequate number of competent scientists in the specialized trainings, but also toward fostering that which was mentioned before, namely, the sound appreciation of science by everyone through early training in its principles. I am referring, of course, not alone to research to serve a particular industry, but also to suggest that the industries might see the largest horizon of serving democracy through making an education in the basic sciences a "must".

And now I end my paper with a quotation from Owen Meredith's "Lucille"

"The age is gone o'er
When a man may in all things be all.
We have more
Analysts, synthesists, and physicists, no doubt
Than old Trismegistus gave birth to
But out
Of a million or more dilettanti, when, where
Will a new Avogadro arise in our ken.
He is gone with the age which begat him.
Our own
Is too vast, and too complex, for one man alone
To embody its purpose, and hold it shut close
In the palm of his hand. There were giants in those
Irreclaimable days; but in these days of ours
In dividing the work, we distribute the powers.
Yet a dwarf on a dead giant's shoulders
Sees more
Than the live giant's eyesight availed to explore."

All of which boils down to the observation that we must so dispose of our todays, in service and in sweat, that they will contribute their worthwhile share to the harvest of the days to come.

THE MICRO-DETERMINATION OF HALOGENS †

By A. J. MonteBovi,* A. Halpern,** H. Koretsky, T. Dunne

THE difficulties involved in the determination of halogens in organic compounds are well-known. Many of the methods described in the literature are cumbersome and time consuming. A fundamental difficulty in these determinations is the conversion of the halogen, bound to the organic nucleus, to the ionic state. In this form its concentration could be conveniently determined either gravimetrically or volumetrically. There are many well-known methods for this digestion involving combustion, oxidation, reduction and other techniques. The Stepanow method (9) and its various modifications has afforded results that were successful where the other techniques had failed (2,3,4,6,10). Rauscher (7), introduced a gravimetric technique based on a modification of the Stepanow method, which is applicable to the micro scale. However, for ease of operation a volumetric procedure is preferred.

The Volhard titration of chlorides is not adaptable to the micro scale because of the errors involved (8). Feldman and Powell (4) adapted the micro-volumetric determination of chlorides, utilizing an absorption indicator. Kolthoff (5) Bobranski (1) and others have used an absorption indicator on the micro scale. Bromphenol blue and the tetrabromphenolphthalein ester gave excellent results.

Recently Sisido and Yagi (8) described a procedure based on a modified Stepanow digestion using an argentometric titration with bromophenol blue as the indicator. This method involves the use of sodium alkoxide as a digesting agent. (Sodium metal and n-butyl, isobutyl or amyl alcohol are used.) The use of aldehyde-free alcohol is a necessity, since the sodium induced polymerization of the aldehydes tends to give the reaction a dark color and obscures the colorimetric end-point. Because of these difficulties it was of interest to examine the possibility of adapting the classical potentiometric-precipitation titration method to this determination. In such a system, the ion concentration at the equivalence point of the precipitation reaction may be determined from the equilibrium constant of the slightly soluble material formed during the titration.

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** Scientific Director, E. Fougera & Co., Inc., N. Y. C.

Precipitation Reactions

From the composition of the solution and the solubility product of the slightly soluble compound formed, the data for the construction of a titration curve is available; since the ion concentration at the equivalence point is determined by the solubility product (S) of the slightly soluble substance formed during the titration. If the salt has the composition BA, then $[B^+] = [A^-] = S$.

The precipitation curve for a salt of the type BA resembles the neutralization curve of a strong acid and base, the solubility product (S) replacing the ion product of water. At the equivalence point

$$[B^+] = [A^-] = \sqrt{S}.$$

The abrupt change of the quotient $\frac{\Delta pAg}{\Delta C}$ (representing the increment of the potential for a given addition of reagent) as seen in Table I and Figure I at the equivalence point reveals the accuracy possible in the titration. The sharpness of this change depends upon the solubility product and upon the dilution at which the titration is made. The smaller the product and the more concentrated the solution, the greater will be the break at the equivalence point.

A modification of the above mentioned method has been developed employing a potentiometric end-point, which can be carried out on a micro scale and the total process requiring less than one hour. The organohalide is fused with molten sodium, the resultant sodium chloride dissolved in water and titrated electrometrically with standardized silver nitrate. It is to be noted that the pH range of the bromophenol blue indicator (used in the Sisido and Yagi (8) procedure) is from pH 3 (yellow) to a pH of 4.6 (blue-violet). The color change becomes increasingly difficult to read above a pH of 4.3, thus decreasing the sensitivity of the determination. In the potentiometric method, by plotting mls. of standard silver nitrate *vs.* millivolts and determining the end-point from the graph, the errors due to overtitration are removed.

Apparatus

A glass tube, 6 cm. x 0.5 cm., 50 ml. beaker, a microburet with 0.05 ml. calibrations, a stirring device, and a suitable potentiometric titration apparatus with silver-silver chloride reference electrode and silver indicating electrode.

TABLE I

TITRATION OF 0.01 N $AgNO_3$ WITH CHLORIDE ($S_{AgCl} = 10^{-10}$)

% of silver precipitated	[Ag +]	pAg	pCl	$\frac{\Delta pAg}{\Delta c}$
0	10^{-2}	2.0	8.0	—
90.0	10^{-3}	3.0	7.0	0.011
99.0	10^{-4}	4.0	6.0	0.11
99.9	1.6×10^{-5}	4.8	5.2	0.89
100.0	10^{-5}	5.0	5.0	2.0
% of chloride in excess				
0.1	6.4×10^{-6}	5.2	4.8	2.0
1.0	10^{-6}	6.0	4.0	0.89
10.0	10^{-7}	7.0	3.0	0.11

Reagents

Silver Nitrate 0.01 N
Acetic Acid, Reagent grade, 10 per cent.
Metallic Sodium
Ethanol, 95%

Procedure

About 0.05-0.075 Gm. of sodium (carefully cut from the inner portions of the block) is melted in the bottom of the glass tube, over a micro-burner, and the sample containing 3-5 mg. of halide is added. (In case of the more volatile halides a longer tube is necessary to serve as an air condenser). The tube is heated intermittently for 3-5 minutes and then to redness for two minutes. When the tube has cooled to room temperature, 0.5 ml. of ethanol is added to react with the excess sodium. This procedure is repeated until no free sodium remains. The tube is then heated cautiously to evaporate any excess ethanol and then to redness for 1-2 minutes. The tube is quenched in a beaker containing 15-20 ml. of water, broken, and the contents washed by swirling. The beaker is heated to boiling for one minute and cooled to room temperature. The electrodes of a suitable potentiometric set-up are introduced into the solution and the stirring started. Acetic acid (10%) is added to acidify the mixture (to a pH below 3). The sample is then titrated with 0.01 N silver nitrate and a

plot made of the mls. of silver nitrate *vs.* mv. (fig. 2). The end-point of the titration is read from the graph and the volume of standard silver nitrate required for the sample determined. The halogen content is then determined in the usual manner.

The results obtained by the use of this method with a series of compounds are presented in Table II.

Summary

A potentiometric technique for the micro-determination of halogens is presented.

TABLE II

EXPERIMENTAL RESULTS OF THE MICRO-DETERMINATION OF HALOGENS

	M.W.	*Halogen %*	
		Cal'd.	*Found* [a]
Bromoacetic Acid [b]	138.96	57.50	57.42 ± 0.20
p-Bromoanisole [c]	187.04	42.72	42.64 ± 0.15
Bromobenzene [c]	157.02	50.89	50.68 ± 0.28
Bromobenzoic [d]	201.03	39.74	39.52 ± 0.31
Bromocamphor [d]	231.14	34.58	34.44 ± 0.17
p-Bromoaniline [b]	172.03	46.45	46.71 ± 0.32
Bromoform [d]	252.77	90.48	90.42 ± 0.04
2,6-Dibromophenol [d]	251.92	63.44	63.41 ± 0.08
2,3 Dibromopropionic Acid [b]	231.89	68.92	68.75 ± 0.15
2-Bromo-1-chloropropane [d]	157.45	73.33 [e]	73.13 ± 0.37
o-Chlorobenzaldelhyde [d]	140.57	24.39	24.31 ± 0.15
2-Chlorobenzothiazole [d]	169.63	20.95	20.92 ± 0.24
Chloromethyl ether [c]	80.52	42.91	42.86 ± 0.07
p-Chlorothymol [c]	184.66	19.25	19.19 ± 0.09
3,4-Dichlorobenzoic Acid [d]	191.02	37.21	36.95 ± 0.41
2,3 Dichlorodioxane [d]	157.00	45.28	45.00 ± 0.36
Dichlorofluorescein [d]	401.19	17.74	17.53 ± 0.35

(a) Average of 4 determinations.

(b) Prepared in our laboratories.

(c) Obtained commercially and purified in our laboratories.

(d) Obtained commercially.

(e) Total Halogen.

Figure 1

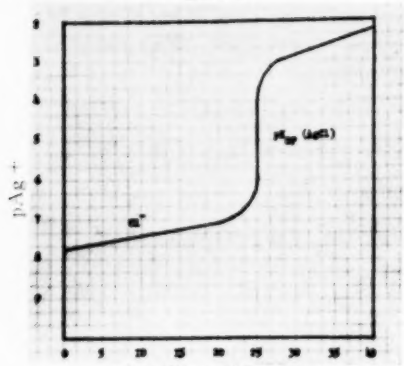
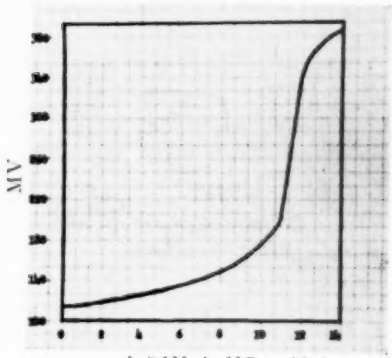


Figure 2



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SELECTED ABSTRACTS

Streptokinase and Streptodornase in the Treatment of Pilonidal Cysts. Miller, J. M., Ginsberg, M., Lipin, R. J., and Long, P. H. *U. S. A. F. Med. J. 2*:1423 (1951). Delayed healing and the incidence of recurrences are primary problems in the treatment of pilonidal cysts. The cysts which are associated with gross infection or abscess present a more difficult problem because the infection must be controlled before a curative operation can be undertaken. Streptokinase and streptodornase have been shown to aid in the preparation of infected cysts for curative operation.

Sixteen patients with abscessed pilonidal cysts were treated by incision, drainage, and the topical application of as much as 100,000 units of streptokinase and 150,000 units of streptodornase a day. Aqueous crystalline penicillin G was also usually given intramuscularly. Such treatment significantly reduced the time required for the infected cysts to become amenable to a curative operation. Of the cases reported the time from incision and drainage to that of operation ranged from 5 days to 2 weeks.

Streptokinase and streptodornase also were found to be valuable postoperatively. Small catheters were inserted laterally to the wound down to the deep fascia over the coccyx. These permit air vent suction to remove accumulations of blood or other products of enzymatic action and permit apposition of the skin flaps to the base of the wound. They also afford a means of placing streptokinase and streptodornase into the wound. These agents help to eliminate factors which permit infection. Streptokinase, by causing fibrinolysis will allow a more satisfactory evacuation of clotted blood, which is an ideal culture media.

An average of 33.7 days was spent in the hospital as compared with an average of 46 days for a series of 17 patients treated for essentially the same condition before the use of streptokinase and streptodornase. The hospital stay under civilian conditions would be materially less since Armed Forces Personnel must be fit for full-time duty when discharged from the hospital.

A Study of the Resistance to Streptomycin of Tubercle Bacilli. Ferebee, S. H. and Appel, F. W. *Pub. Health Rep. 66:* 277 (1951). The importance of the development of bacterial resistance to streptomycin depends not only on the frequency with which resistance develops in the cultures remaining positive but also on how frequently cultures continue, in spite of drug therapy, to remain positive. The bacteriological course for 157 patients who were treated with streptomycin for 91 days was followed for 53 weeks. At the beginning of the study the entire group had positive cultures sensitive to streptomycin. The streptomycin was given on the regimen of 20 mg. per day per Kg. of body weight in 3 equally divided doses. The number of cultures in which tubercle bacilli were not detected gradually increased until 40 per cent had negative cultures at the end of the 53 week period. Five per cent of the patients were dead and the remaining 55 per cent were still excreting tubercle bacilli, about two-thirds of which were moderately or strongly resistant to streptomycin.

In the majority of patients the development of resistance occurred during the period of adminitration of the streptomycin. Once the bacilli became resistant this resistance tended to persist after the cessation of therapy. However, about 18 per cent of the patients showed reversion to streptomycin sensitivity. The authors pointed out that the development of streptomycin resistance in the tubercle bacilli, particularly those which become highly resistant, may appear to prejudice the chances of the patient to cease producing positive cultures. However, they emphasized that the cause and effect relationship is not yet clear. It may well be that resistant organisms are found because the individuals do not respond well initially to therapy and, therefore, continue to excrete tubercle bacilli.

A Field Trial of Methadone and Levo-Iso-Methadone. Beecher, H. K., Deffer, P. A., Fink, F. E., and Sullivan, D. B. *U. S. A. F. Med. J. 2:*1269 (1951). Since there is a possibility that the natural source of supply of opium and its derivatives may be cut off there has been an extensive study to try to find a readily synthesized compound which could be used to replace morphine in such an eventuality. Methadone and levo-iso-methadone have proven to be the best compounds found thus far. In order to be sure that field

conditions do not introduce problems unforeseen under civilian testing the authors conducted a field study on Korean combat victims at both front line and base hospital levels.

The field trials confirmed the previous findings in civilian hospitals. The method of evaluation of the pain-relieving effect was simply the questioning of patients under steady pain at 45 and 90 minutes after the administration of the medication, a method that had proven to be surprisingly satisfactory. The combined pain-relieving effects at the two combat hospital levels was 90 per cent relief with racemic methadone, 79 per cent was levo-iso-methadone, and 79 per cent with morphine. The dosage employed was 15 mg. of each drug at the front line hospital and 10 mg. of each at the base hospital. At the front line it was also found that 5 mg. of morphine with 50 mg. of pentobarbital was just as effective an analgesic as was 15 mg. of morphine alone. Thus it was shown that under field conditions, as had previously been established under civilian trial, both forms of methadone are equally effective in analgesic power, mg. for mg., with morphine. It was also confirmed that 10 mg. of morphine will give as much pain relief as will 15 mg., with less undesirable side effects.

The side effects with the racemic methadone were also confirmed as being equivalent to morphine. The hypnotic effect was also found to be essentially equivalent. However, there was less nausea and vomiting following the use of levo-iso-methadone than with either morphine or racemic methadone.

Tuberculous Meningitis Treated With Streptomycin. Illingworth, R. S., and Lorber, J. *The Lancet* 2:511 (1951). Streptomycin was used in the treatment of 82 consecutive cases of tuberculous meningitis some of whom were moribund on admission. Thirty-six children survived, an over-all rate of 43.9 per cent. The survival rate in cases diagnosed and treated early was 73.7 per cent and in advanced cases was 34.6 per cent. There was no significant difference in the survival rate when the meningitis was associated with or without clinical evidence of miliary tuberculosis.

The follow-up among the survivors of this series, including physical, radiological, audiometric, and psychometric tests, revealed that 61.1 per cent had no residual physical or mental defects, 11.1 per

cent had some physical defect but were mentally normal, and 22.2 per cent were mentally retarded with or without physical defects. Of the 27 survivors in the early or intermediate stages 25 retained normal intelligence but only 3 of 9 survivors who were in advanced stages retained normal intelligence.

The treatment underwent changes as the series of cases progressed. The routine which was used at the end of this study was a continuous series of 42 daily intrathecal injections for six days each week, of 25 mg. of streptomycin for children under 3 years of age, 50 mg. for those between 3 and 9, and 75 mg. for those over 9 years of age. A rest period of 1 week after the first 21 injections was discontinued because of its possible contribution to the rapid deterioration in a few children. After 42 injections this therapy was discontinued if no tubercle bacilli had been recovered from the cerebrospinal fluid for the 6 weeks previous and if the cerebrospinal fluid cell count one week after the last injection was at or approaching 100 per cu. mm. Intramuscular streptomycin was also given in daily doses of 20 mg. per lb. of body weight in divided doses, continuously, for six months together with 0.5 Gm. of para-aminosalicylic acid orally per Kg. of body weight. Intrathecal tuberculin (purified protein derivative) was also given in advance cases. Sulphetrone gave no evidence of having value when used as an adjunct.

Use of Chlorophyll in Medicine. Westcott, F. H. Paper delivered at the First International Congress of Allergists at Zurich, Switzerland, Sept. 26, 1951. The author reviewed the development of the medical interest in chlorophyll since about 1916. He emphasized the several reports on the use of chlorophyll in the management of body and breath odors. Reference was also made to the combination of chlorophyll fractions with antacids as adjuncts in the relief of peptic ulcer symptoms and as aids in the healing of these ulcers by stimulating granulation tissues.

The author then reported personal studies on the use of chlorophyll fractions in the treatment of allergic rhinitis and seasonal hay fever. The fractions used were the special chlorophyll fractions called chlorophyllins prepared by treating fresh leaf extracts with sodium hydroxide. Chlorophyll then yields phytols and the alkali salts of carboxylic acids called chlorophyllins. These chlorophyllins were com-

bined with calcium gluconate and sodium bicarbonate in the treatment of 36 cases. Of this group 55 per cent showed improvement and 45 per cent remained the same. The next year 33 patients were treated with a similar combination differing in that the sodium bicarbonate was replaced with ascorbic acid. Of this group 78 per cent showed symptomatic improvement. Later ephedrine was added to the latter combination and a group of 60 hay fever patients treated with this combination showed improvement in 87 per cent of the cases.[4] The cases treated were the more severe cases who were not relieved of their symptoms by hyposensitization.

The author pointed out that the particular advantage of the use of chlorophyllins in combination with calcium, as ascorbic acid, and ephedrine over the anti-histamine drugs for the symptomatic relief from seasonal and non-seasonal allergic rhinitis lies in the absence of drowsiness, gastritis, headache, and other disagreeable side effects.

New Vehicles for Administering and Controlling the Action of Therapuetic Agents. Ouer, R. A. *Ann. Allergy* 9:346 (1951). The sodium, potassium, ammonium and calcium salts of alginic acid and its propylene glycol ester in aqueous solution were found to be stable within a wide temperature range, relatively constant in activity, easily absorbed, and safe, non-toxic vehicles for therapeutic agents by parenteral administration. In rabbits no toxic reactions were evident from the intraperitoneal injection of up to 375 mg. per Kg. of propylene glycol alginate (PGA). The solutions were made isotonic with sodium chloride and contained 0.05 per cent chlorobutanol or 0.45 per cent phenol and 0.01 per cent sodium bisulfite.

When used as a vehicle for epinephrine HCl, PGA slowed down the rise and fall in blood sugar levels normally obtained with epinephrine. The blood sugar levels in fasting rabbits rose to a maximum of 128 mg. per cent with 1:1000 epinephrine HCl. When combined with 1.5 per cent PGA the maximum level was 102 mg. per cent. Higher concentrations of the ester considerably reduced the activity and decreased the rate of absorption of epinephrine HCl. The maximum blood sugar levels were 120 mg. per cent with 1:200 epinephrine HCl plus 0.8 per cent sodium alginate, 86 mg. per cent with 1:500 epinephrine HCl in 2.25 per cent PGA, and 98 mg. per cent with 1:500 epinephrine in oil.

The combination of 2 per cent PGA with 20 units of insulin prevented the rapid fall of blood sugar and death from insulin shock which the insulin would normally produce in a rabbit. The author also reported that the effect of these vehicles on pulse rate, respiratory rate, nervousness, etc., closely paralleled the effect on the blood sugar.

A New Series of Anti-Malarial Compounds, 2,4-Diaminopyrimidines. Falco, E. A., Goodwin, L. G., Hitchings, G. H., Rollo, I. M., and Russell, P. B. *Brit. J. Pharmacol. Chemother. 6:* 185 (1951). A series of 2, 4-diaminopyrimidine derivatives were tested for antimalarial activity against *Plasmodium gallinaceum* in chicks and against *P. berghei* in mice. The only compound in the series which was effective against the test parasites in concentrations as small as 0.1 and 0.01 mg. per Kg. was 5-(p-chlorophenyl)-2, 4-diamino-6-ethyl pyrimidine (50-63). This compound was found to be 60 times as active as proguanil (chlorguanide) against *P. gallinaceum* and 200 times as active against *P. berghei.* A test was performed on two monkeys infected by mosquito bite with *P. cynomolgi,* one of which served as a control and the other of which was treated with 5 mg. per Kg. of 50-63 by injection twice a day for 4½ days beginning 7 days after infection. No parasites appeared in the blood of the treated animal until the 30th day after infection while they appeared on the 13th day and persisted for 12 days in the control animal.

A second compound, 5-(p-chlorobenzyl)-6-methyl-2, 4-diaminopyrimidine (49-224), was found to be active in doses of 10 mg. and 1 mg. per Kg. in chicks. It was 0.4 times as active as proguanil against *P. gallinaceum* and twice as active against *P. berghei.* When tested by mosquito bite infection in one monkey 40 mg. per Kg. of 49-224, given the 4th day after infection, did not prevent the appearance of parasites in the blood on the 10th day after treatment. Subsequent administration of 4 mg. per Kg. twice a day for 5 days beginning 14 days after infection cleared the blood but did not prevent relapse 4 weeks later. In one other monkey the administration of 2 doses of 20 mg. per Kg. of 49-224 1½ hours before infection did not prevent the appearance of the parasites in the blood 14 days later.

The authors also reported that the LD_{50} for compound 50-63 in mice was 92 mg. per Kg. and that of compound 49-224 was 79 mg. per Kg.

Mode of Action of Histamine Desensitization. Ambrus, J. L., Ambrus, C. M., and Harrisson, J. W. E. *Am. J. Physiol. 167:268-275* (1951). Histamine desensitization has long been practiced in clinical medicine; however, little was known about the mode of action of this phenomenon. The authors have shown that the degree of desensitization is proportional to the total dose of histamine administered and largely independent from the time over which it is given. In fact, a single large dose of histamine given under the protection of an antihistamine drug is able to confer desensitization upon experimental animals, which becomes manifest after the effect of the antihistamine has ceased.

In the organs of desensitized animals, no antihistamine factor could be found nor did the decomposition products of histamine (prepared *in vitro* by incubation with a purified histaminase preparation) exhibit any antihistaminic potency.

In the organs of desensitized animals, however, a high histamine content was evidenced. This histamine seems to be in an inactive, probably complex form.

On the basis of these data, the following theories are advanced to explain the mechanism of histamine desensitization: The inactive histamine complex occupies probably the cellular histamine receptors, thus inhibiting the effect of further doses of histamine; or the high inactive histamine content of the cells bars the diffusion of further doses of this substance according to the potential theory of Straub.

Toxic Effects of Diaminodiphenylsulfphone in Leprosy. Allday, E. J. and Barnes, J. *Lancet 2:205* (1951). One hundred fifty-three cases of leprosy of all types were treated for periods varying from 2 to 8 months with diaminodiphenylsulfphone (DADPS). The daily oral dose of the drug was 100 mg. for the first two weeks and this was then gradually increased until 200 mg. was being given.

The toxic effects manifested were DADPS syndrome in 7, lepra reaction in 6, psychosis in 1 and neuritis in 1. The DADPS syndrome was thought to be due to hypersensitivity and was manifested by a group of symptoms. Following 5 or 6 weeks of treatment a violent illness suddenly appeared with a papular or exfoliative rash. This was followed by enlargement and tenderness of the liver, epigastric pain, jaundice, swelling of the lymph glands, and mononucleosis (70

per cent lymphocytes and monocytes). For about 2 weeks these conditions persisted and then slowly progressed toward healing or death (one case). The one case of psychosis gave no familial history of mental disorder and so it may have been of toxic origin. The other symptoms were the same as those often encountered in the natural course of leprosy.

Because the oral administration of a drug for the control of leprosy has such an advantage the authors tried another series of patients in which 100 mg. per day was given. However, the DADPS syndrome again appeared and so the authors concluded that this drug is too toxic for use in the treatment of leprosy.

The Stability of Vitamin A in High Potency Concentrates. Debodard, M., Matet, J., Nicolaux, G., and Stuckey, R. E. *J. Pharm. Pharmacol. III*:631 (1951). Vitamin A is susceptible to the action of air, light and heat and its susceptibility to oxidation is of particular practical importance. The authors studied the stability of vitamin A to oxidation by diluting the concentrates to a uniform potency of 10,000 I. U. per Gm. and then bubbling oxygen at a uniform rate through the dilution in a standard container at 96° C. The destruction of the vitamin was followed by spectrophotometric assay. The index of stability was defined as the time in hours required for the destruction of 50 per cent of the original vitamin A content. The uniform dilution of 10,000 I. U. was selected because it was found that the concentration of the vitamin had a marked effect on the index of stability. Higher concentrations had a much lower index of stability.

The concentrates studied included those obtained by saponification of liver oils with the vitamin in the form of the alcohol, by chromatography, by selective extraction, by molecular distillation, by molecular distillation followed by saponification and acetylation, and those containing synthetic vitamin A or vitamin A palmitate. Eight out of the 18 different samples studied were of synthetic origin. Their stability in general was very low. Only one exceeded an index of stability of 5 and six of the eight were below 3. The alcohol form of the vitamin also was of low stability, having an index in the range of that of the synthetic forms of the vitamin. Thus the previous contention was verified that vitamin A as the ester is more stable than is the alcohol. The samples of natural vitamin obtained by molecular

distillation gave the highest consistent stability. The four samples obtained by this method showed a stability index varying from 12.4 to 17. The authors stated that the high degree of stability shown by concentrates obtained by molecular distillation may be explained by the fact that the antoxidants initially present in the natural oils are found after distillation in the same fractions as the vitamin A. This raised the question as to whether or not the addition of antoxidants would improve the stability of the other concentrates under the test conditions. Several antoxidants among them DL-α-tocopherol, ional, and hydroquinone-citric acid, were tried but only a very slight improvement was obtained. However, the authors noted at this point that crystalline vitamin A acetate can be given a stability index of 10.6 when antoxidants are added.

The authors concluded that the poor stability of several of these forms of vitamin A, particularly the synthetic forms, was not due to a lack of antoxidants but rather to the presence of some unknown substances which act as pro-oxidants.

Nitrogen Mustard Therapy of Rheumatoid Arthritis. Diaz, C. J., Garcia, E. L., Merchante, A., and Perianes, J. *J. A. M. A. 147*:1418 (1951). A preliminary report was made by the authors with respect to the striking results which were obtained in 9 patients with rheumatoid arthritis who were treated with nitrogen mustard. No comparative study was made with ACTH and Cortisone.

The first patient treated with the nitrogen mustard had had rheumatoid arthritis for 11 years and had been bed fast for 5 years. An injection of 6 mg. of the nitrogen mustard produced no obvious results but the second injection brought about striking changes. The pain was almost completely relieved, the swellings of the joints were reduced considerably and movement was so improved that the patient was able to get up out of bed and walk. After the 4th injection the patient was able to move her arms and legs with perfect ease and the painful symptoms had disappeared with the exception of a slight ache in one knee. One month later the patient's condition was still satisfactory. A second patient had ankylosis of the hip joints and lumbar part of the spine and painful swellings of the other joints. He also became essentially free of pain after the second injection and regained movement of the swollen joints but, as was to be expected, the

ankylosis was not improved. Two months after the treatment had been stopped the improvement was still evident.

Seven additional patients were treated in like manner with similar results. Two of the latter group showed only relief of pain and reduced swelling of joints because of bony ankylosis in one and irreversible muscular retraction in another.

Striking improvement was also obtained in two patients with prolonged status asthmaticus.

The authors found that the striking effects of the nitrogen mustard on the rheumatic condition paralleled the effects on the blood picture. There was a fall in eosinophils from an initial count of 100 to 200 to 20 to 50 after about the 3rd injection. The lymphocytes also decreased progessively. The sedimentation rate was found to increase initially and then fall, but it never seemed to return to normal low levels.

The authors pointed out that although these results were strictly preliminary they were so striking that a report was being made in order to stimulate investigation on the part of others.

The Role of Ascorbic Acid in Tyrosine Oxidation. Sealock, R. R. and Goodland, R. L. *Science 114*:645 (1951). The chemistry of the biological functions of ascorbic acid has not heretofore been adequately explained. However, the authors have found that ascorbic acid acts as a necessary coenzyme in the metabolic oxidation of tyrosine.

Liver slices from normal guinea pigs were able to oxidize tyrosine as shown by the manometric measurement of oxygen consumption. However, liver slices from scorbutic guinea pigs were not able to oxidize tyrosine unless the crystalline vitamin was added. Upon the addition of the vitamin the oxygen consumption was indistinguishable from that of the liver slices from normal guinea pigs. Further studies showed that α-ketoglutaric acid is necessary as the amino group acceptor in the first stage of the reaction, a transamination reaction. When appropriate solutions of enzymes with the necessary additives where incubated with tyrosine the addition of ketoglutaric acid in stoichiometric proportions and ascorbic acid in catalytic quantities, caused the oxidation of tyrosine with the uptake of 4 atoms of oxygen per mole of tyrosine present. Without the

vitamin less than 1 atom of oxygen was consumed. They also found that the velocity of the oxidation is dependent upon the concentration of ascorbic acid present.

The exact mechanism of the chemical reaction is not known but the authors postulated that the enzyme removes hydrogen from the tyrosine keto acid by means of the dehydroascorbic acid form of the vitamin, with a subsequent transfer of the hydrogen to an oxygen atom and the regeneration of dehydroascorbic acid.

The Use of Silicone Water-Repellants for General Use in the Laboratory. Gilbert, P. T., Jr. *Science 114*:637 (1951). When the water-repellant silicone films are applied to pipettes, burettes, beakers, flasks, and other types of analytical glassware a great saving in time and increase in accuracy is obtained by making drainage complete and eliminating the rinsing, washing and drying. Substituted chlorosilanes, such as methyltrichlorosilane, apparently are adsorbed to the surface of the glass in monomolecular layers. The polar Si-O bonds apparently exhibit an affinity for the similarly constituted structure of the glass surface, and the organic radicals, directed outward, provide the water-repellency.

Glass surfaces must be completely clean and dry in order to be coated well. Best results may be obtained by the use of the silane dissolved in an inert volatile solvent such as benzene or carbon tetrachloride. Accessible areas of the glass are rubbed with a few drops of the silane solution on tissue paper. Inaccessible areas are coated by filling, rotating or pouring. Once applied the film is permmanent for at least 3 years. Apparently the only solvents that will attack the film are those that will attack glass, such as strong alkalies and hydrofluoric acid. Vessels should be filled and emptied with care, for air bubbles impinging on the submerged wall of a coated vessel will stick relentlessly, as also will droplets striking the wall above the water level or "tails" of liquid left in the corners of vesses having corners or small radii of curvature. Careful moving of the body of liquid to encompass these stray portions is the best way to eliminate them.

Volumetric ware calibrated to deliver becomes more precise because there is no residue subject to unreproducible drainage. Volumetric ware graduated to contain may then also be used to deliver. Coated glass rods carry no liquid with them, there will be no loss

from dribbling of solutions or suspensions down the outside of containers when the pouring lip is coated, and droppers will deliver smaller and neater drops when the tip is coated. In spectrophotometry the absorption cells are more easily cleaned and carry-over contamination is almost entirely eliminated. In pH work coated glass electrodes reduce carry-over and provide more rapid and more reproducible equilibrium at the liquid junction. Potassium chloride incrustations are reduced because coated calomel electrodes reduce creeping.

The Effectiveness of Various Antibiotics on Endamoeba Histolytica. Felsenfeld, O., Kadison, E. R., Ishihara, S. J. *Am. J. Pub. Health 41*:1078 (1951). Several of the newer antibiotics were studied for their amebicidal activity against *E. histolytica*. Tests were made *in vitro, in vivo* in mice, and clinically in man. The antibiotics studied included penicillin G, allylmercaptomethyl penicillin, 1,2-diethyl-2-diaminoethanol penicillin, aureomycin, Chloromycetin, Terramycin, neomycin, bacitracin, fradicin, prodigiosin, polymyxin D, and streptomycin.

All of the antibiotics with the exception of streptomycin and polymyxin were active against the organisms *in vitro*. The 3 forms of penicillin and fradicin were found to be active but only in concentrations higher than that normally attained in the intestine. Aureomycin, chloromycetin and terramycin caused the appearance of numerous cysts in the cultures when employed in subinhibitory concentrations.

Since it is known that in man amebiasis is nearly always associated with additional lesions caused by secondary invaders, the authors tried several combinations of antibiotics which could be expected to reduce all components of the intestinal flora and at the same time inhibit the amebas. A combination of 1,000 to 4,000 units of neomycin and 250 to 500 units of bacitracin per Kg. per day for 10 to 14 days proved to be the best combination. The course was repeated after an interval of 1 week, if necessary. After 3 to 6 months' observation, 41 out of 48 patients with amebiasis treated with this regimen did not show relapses. Forty-seven cases of infantile diarrhea were also cured with this combination.

No difficulties were experienced in the treatment of these patients. However, the authors warned that a careful control of such therapy

must be carried out. It is well known that many of the bacteria in the intestine have highly important functions with respect to their host and that drastic reductions in these organisms for a prolonged period may cause serious deficiencies or reactions.

Buccal Androgen Alone and With Estrogen in Tension and Anxiety States. Newman, G. T. *Am. J. Obst. Gynecol.* 62:607 (1951). Two groups of patients were treated by the author, all suffering from tension and anxiety. The first group contained 19 patients with symptoms resulting from hyperestrinemia as indicated by vaginal smears. This group was treated with androgen alone in the form of buccal tablets of testosterone propionate. The dosage varied from 75 to 100 mg. a month for 3 patients to 150 mg. for 15 patients and even 300 mg. for 1 patient. After at least 2 months' therapy the cornification of vaginal smears was reduced from 80 to 100 per cent to less than 20 per cent in 15 cases. The clinical results, based upon definite improvement or complete relief of tension and anxiety, was excellent in 12, good in 4, fair in 2 and poor in one.

The second group of 20 patients had been under treatment for hypo-ovarian symptoms of the menopause but tension and anxiety had not been adequately controlled by estrogen alone. Therefore, a combination of estrogen and androgen was given to these patients. The estrogen employed was crystalline estradiol parenterally in 14 patients and oral estrone sulfate in 6 patients. Testosterone was given buccally in 18 patients and parenterally in 2 patients. All of the patients except one experienced more marked relief with the combination than with the estrogen alone. With estrogen alone relief of symptoms occurred at a vaginal smear level of 20 to 100 per cent cornification. With the combined therapy the patients felt well when the vaginal smear level was reduced to 10 to 0 per cent cornification. The author, therefore, stated that the vaginal smear is not a reliable index of the clinical results. The ratio of the estrogen to androgen varies with a number of factors, i.e., potency of hormones, route of administration, activity of the ovaries and the activity of the adrenal glands. In this series it was found that 4 mg. of crystalline estradiol per month was neutralized by 160 mg. of buccal testosterone propionate, as evidenced by the reduction of cornification in vaginal smears to menopausal levels. By parenteral injection testosterone propion-

ate gave a neutralizing level of 1:20. With estrone sulfate and buccal testosterone the neutralizing ratio was found to be from 1:2 to 1:7.

The author concluded that the use of androgen alone and with estrogen has a definite place in gynecologic therapy and that this field should be further investigated.

The Polyanibiotic Treatment of Pulpless Teeth. Grossman, L. I. *J. Am. Dental Assoc. 43*:265 (1951). A paste made up of 1,000,000 units of potassium penicillin G, 10,000 units of bacitracin 1 Gm. streptomycin-Calcium chloride, and 1 Gm. sodium caprylate in 3 cc. of a silicone fiuid with a viscosity of 20 centistokes sterilized root canals more rapidly and more effectively than other known methods, according to the author. Two hundred fifty teeth were treated in a like number of patients.

Cultures were found to be negative after but one treatment in 162 patients, after 2 treatments in 71 patients, after 3 in 14 and after 4 treatments in 3 patients. Periapical irritations were no more frequent than with other types of medications and severe or mild periodontitis occurred in only 8 patients. In these patients treatment was resumed after the symptoms subsided. Except for edema in one patient, which lasted only a few hours, no allergic reactions were noted and no bacterial resistance was evident. Toxicity tests on rabbits gave no evidence of inflammation when the polyantibiotic preparation was injected subcutaneously daily for up to 2 weeks. However a nodule persisted for 10 days, indicating slow absorption of the material.

Sterile Proteolytic Enzyme Preparations in Dental Practice. Bullock, K. and Sen, J. K. *J. Pharm. Pharmacol. 3*:756 (1951). The use of proteolytic enzymes to liquefy the necrotic tissue and to leave a sterile, clean root canal cavity for the subsequent operation of root canal filling was suggested several years ago. Papain showed particular promise but the difficulty in obtaining an enzyme preparation free from bacteria had left considerable doubt as to whether the digestion of the necrotic tissue in the root canal was due to the action of the enzyme or to the action of associated proteolytic bacteria. Therefore, the authors sought to prepare papain and pancreatin in a form free from bacteria.

Since the metabolic processes of bacteria are mainly brought about by the mediation of enzyme systems the problem was to so alter the protein of the bacterial enzymes so that life was impossible without damaging the papain and pancreatin. Both dry heat for 1 hour at 130° C. with the enzymes as dry powders and moist heat for 40 minutes at 55° C. showed a loss in activity of about 50 per cent. Sterilization by filtration through a Doulton filter candle was not possible since most of the enzyme was retained by the filter candle. It was found that pancreatin could be sterilized by filtration through either a Seitz filter or a 5/3 sintered glass filter, with little loss of activity. However, the Seitz filter removed most of the papain from the solution until the adsorption characteristics of the pad for the enzyme were satisfied. Then, the rate of filtration was markedly reduced. Thus the 5/3 sintered glass filter was found to be the only satisfactory way to sterilize solutions of these enzymes. Sterility of the filtrates was verified by repeated sterility tests. When sealed aseptically in ampuls and stored in a refrigerator these filtrates maintained their activity for at least 2 months. The papain preparation contained cysteine as an activator and chlorocresol as a bacteriostatic agent. A sterile powder was prepared by spray-drying the solution.

The papain preparations were found to be very effective in digesting the necrotic tissue *in vitro* but not the pancreatin, even though the latter is of high tryptic activity. *In vivo* trials in tooth cavities are still in progress.

Changes in Solutions of Procaine Hydrochloride and Dextrose. Cannell, J. S. *J. Pharm. Pharmacol. 3*:741 (1951). It was observed that solutions for injection containing procaine hydrochloride and dextrose gradually changed in optical rotation from the expected rotation based upon the amount of dextrose present to a rotation opposite in sign to that of the freshly-prepared solution. Further investigation showed that similar changes occurred in solutions containing procaine hydrochloride and other aldoses. Likewise, similar changes were found to occur with dextrose and other local anesthetic amines having a primary amine group.

It was found that in these solutions condensation occurs between the primary amine and the aldose to form N-glycosides. The procaine N-(D)glucoside was isolated and characterized. This compound had not previously been described but the type reaction involved is well

known. It occurs in small colorless crystals having a melting point of 140° to 141° C., it is readily soluble in water, and its aqueous solutions are laevororotatory and show mutarotation, the equilibrium rotation being —74.0°.

The chemical significance of this finding is that before the analytical determination of either the aldose or the aglycone the glycoside must be subjected to hydrolysis. The pharmacological significance has not yet been investigated. However, since solutions of procaine hydrochloride and dextrose continue to give satisfactory clinical results it may be assumed that the action of the glycoside closely resembles that of the procaine itself.

Chloramphenicol Therapy in Meningitis. McCrumb, F. R., Hall, H. E., Merideth, A. M., Deane, G. E., Minor, J. V., and Woodward, T. E. *Am. J. Med. 10*:696 (1951). The authors verified previous findings that chloramphenicol was effective *in vitro* and *in vivo* against *Neisseria intracellularis*. *In vitro* tests showed that the range of activity of chloramphenicol was from 0.62 to 2.5 gamma per cc. *In vivo* studies in mice showed that chloramphenicol, aureomycin, penicillin, sulfadiazine, and terramycin were all very effective in controlling the infection. The results obtained with each of these compounds was roughly comparable.

Fifteen infants and adults with meningococcal meningitis were treated with chloramphenicol. In all 15 patients the antibiotic produced a rapid return of the temperature to normal regardless of the severity of the disease or the age of the patient. The temperatures reached normal on an average of 3.5 days with a range of 1 to 4.5 days. There was a remarkable improvement in the appearance of the patients within the first 24 hours of treatment and the headache had largely abated.

The chloramphenicol was administered orally to children of all ages in doses of approximately 0.25 Gm. every 4 hours and to adults in doses of 1 Gm. every 8 hours, following an initial dose based upon 50 mg. per Kg. of body weight. In an effort to obtain a prompt high therapeutic blood level chloramphenicol was administered intravenously to a few patients until oral therapy was practical. The usual dose for adults intravenously was 0.5 Gm. every 6 hours. Children received approximately half the adult dose. The total amount of antibiotic administered to these 15 patients varied from 5.5 to 30 Gm.

The mean period of treatment was 5.6 days with a maximum period of 9.5 days. In all instances in which blood serum and spinal fluid concentrations were determined adequate levels were found whether the patient was being treated orally or intravenously. The levels of the antibiotic in the spinal fluid were roughly 1/3 to 1/2 those of the blood.

Plasmodium Malariae Infections Treated With Three Different Drugs. McLendon, S. B. and Young, M. D. *J. A. M. A. 147:822* (1951). Malaria infections were induced in 33 neurosyphilitic patients by the intravenous injection of parasites of the U. S. Public Health Service strain of *P. malariae*. The number of fevers experienced by the patients varied from 1 to 35 before therapy for the control of the infection was instituted. Parasite densities at the beginning of therapy ranged from approximately 1000 to approximately 30,000 per cubic millimeter of blood.

The efficacy of three anti-malarial drugs was studied on these patients. Ten patients received 0.5 Gm. metachloridine orally every 6 hours for 6 days. Seven patients received 0.1 Gm. chloroguanide (Paludrine) orally 3 times a day for 10 days. Chloroquine dihydrochloride was given to 4 patients in a single intramuscular injection of 225 mg. in 5 cc. of solution and to 12 patients in a single intramuscular injection of 450 mg. in 10 cc. of solution.

Neither metachloridine nor chloroguanide gave very satisfactory results. The median time for disappearance of the parasites from the peripheral blood was 12 days in both groups. However, fewer patients had fever episodes following therapy with chloroguanide than with metachloridine. An unsatisfactory response was obtained with the 225 mg. dose of chloroquine dihydrochloride. One patient became negative to a parasite count but relapsed later. The other three patients showed only a temporary diminution in the number of parasites. The 450 mg. injection of chloroquine dihydrochloride gave the best results with the most rapid elimination of the parasites from the blood stream. The median time for this was 5 days. The fevers were also eliminated more rapidly. Five patients in the latter group had no fevers following the institution of therapy and the other 7 had but one fever each. The patient having the highest parasite density in the peripheral blood prior to therapy was in this group. No toxic reactions to any of the drugs was observed.

BOOK REVIEWS

Selective Toxicity With Special Reference to Chemotherapy. By Adrien Albert; 228 pages incl. index. London: Methuen & Co. Ltd., New York: John Wiley & Sons, Inc., 1951. Price $1.75.

This most interesting and well written little book is based on a series of post graduate lectures given by the author at the University College, London, in 1948 and 1949 and it is one of several monographs on biochemical subjects available from the same publishers.

The book is concerned with the means and mechanisms by which selectively toxic agents act. Substances included among these agents are drugs, weed killers, insecticides, etc. A partial list of subjects covered includes: What is selective toxicity?, the nature of the drug receptor bond, how chemically inert substituents can influence biological action, metabolite analogues, the covalent bond in relation to selective toxicity, the role of ionization in selective toxicity, chelation phenomena and the living cell and selective toxicity in relation to pharmacology.

Dr. Albert's book is particularly useful to those not specialists in biochemistry but who have more than a passing interest in its important discoveries. Graduate students and research workers in pharmacy and pharmacology should find in it very valuable and interesting reading. The author is to be complimented for its clarity of presentation.

L. F. Tice

Statistical Methods for Chemists. By W. J. Youden. John Wiley & Sons, Inc., New York, N. Y. 126 pages. $3.00.

The object of the author has been to present to those scientists, especially chemists, who make measurements and interpret experiments some practical applications of the more important statistical techniques. Statistical theory and proofs of the applicability of techniques have been omitted, it being assumed that the experimenter in-

stinctively sees that the formulations of the statistician are in accord with the former's experience.

The ten chapters of the book consider the following topics: (1) Precision and Accuracy; (2) The Measurement of Precision; (3) The Comparison of Averages; (4) The Resolution of Errors; (5) Statistics of the Straight Line; (6) The Analysis of Variance; (7) Interaction between Factors; (8) Requirements for Data; (9) Arrangements for Improving Precision; (10) Experiments with Several Factors.

Not only chemists, but scientific experimenters generally, will find this book highly useful in helping them to interpret the results of experiments more meaningfully and to design experiments more logically.

ARTHUR OSOL

Bentley and Driver's Text-Book of Pharmaceutical Chemistry, Fifth Edition. Revised by J. E. Driver; 671 pages incl. index. Geoffrey Cumberlege Oxford University Press; London, New York and Toronto, 1951. Price $7.25.

This is a well known English text of Pharmaceutical chemistry, having been used for a number of years by students preparing for examinations in this subject in Great Britain and other parts of the British Empire. This, the fifth edition, has been revised to bring it in conformity with the British Pharmacopeia, 1948.

The text is arranged in four parts titled: Analytical Methods, Inorganic, Organic and Appendices. The subject matter is prepared with the assumption that the student has had the necessary preliminary courses in chemistry and the emphasis is placed on pharmaceutical substances. Analytical procedures and tests for purity are given primary consideration, although structure and preparation are also included.

There is close similarity in the list of official substances in the B. P. and the U. S. P. This text should prove a useful reference in the United States, particularly in laboratories concerned with pharmaceutical control.

L. F. TICE

Ultraviolet Spectra of Aromatic Compounds. By Robert A. Friedel and Milton Orchin. John Wiley & Sons, Inc., New York, N. Y. 708 pages. $10.00.

This book is primarily a collection of 579 ultraviolet absorption spectra, arranged according to the increasing number of condensed aromatic rings in the respective compounds (unsaturated heterocyclic rings are here regarded as aromatic rings). The emphasis is on polynuclear hydrocarbons. Spectra of many of the compounds known to occur in coal tar and shale oil are included, as are also spectra of numerous cancer-producing compounds. Spectra of aliphatic compounds, dyes, sterols and steroids, hormones, vitamins and alkaloids are among those not included.

A section of 34 pages of text material discusses such subjects as spectrometric nomenclature and the absorption law, instruments and experimental procedure, theoretical aspects of ultraviolet absorption spectra, and the use of ultraviolet absorption methods in qualitative and quantitative analyses.

The spiral binding of the book permits removal of the pages and superimposition of the uniformly plotted spectra for purposes of comparison; spectra are printed only on one side of each leaf. All of the pages may be transferred to a conventional three-ring notebook binder, for which usage they have been suitably punched.

ARTHUR OSOL

Organic Reactions. Volume VI. Roger Adams, Editor-in-chief. viii + 517 pages. John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y., 1951. Price $8.00.

This is a continuation of a most useful series of volumes. As is usual, the reactions are discussed in great detail and include mechanism, modifications, experimental conditions, applications, specific procedures, and, finally, complete tables of the literature surveyed. Conveniently, each chapter gives the date to which the survey has been carried. These dates range through 1946 to January, 1950. There are a number of 1950 references in at least one chapter and at least one 1951 reference.

The 10 topics discussed in this volume are:

1. The Stobbe Condensation
2. The Preparation of 3, 4-Dihydroisoquinolines and Related Compounds by the Bischler-Napieralski Reaction.
3. The Pictet-Spengler Synthesis of Tetrahydroisoquinolines and Related Compounds
4. The Synthesis of Isoquinolines by the Pomeranz-Fritsch Reaction
5. The Oppenauer Oxidation
6. The Synthesis of Phosphonic and Phosphinic Acids
7. The Halogen-Metal Interconversion Reaction with Organolithium Compounds
8. The Preparation of Thiazoles
9. The Preparation of Thiophenes and Tetrahydrothiophenes
10. Reductions by Lithium Aluminum Hydride

N. RUBIN

Organic Syntheses, Volume 31. Edited by R. S. Schreiber. Published by John Wiley and Sons, Inc., 440 Fourth Ave., New York 16, N. Y., 1951. v + 122 pp. 15.5 x 23.5 cm. Price $2.75.

The new volume of the very familiar series is written in the typical style of all the preceding works. Volume 31 contains forty-two preparations. Of these, two methods are given for the preparation of aryl ureas; the cyanate and the urea methods. Optimum conditions for the syntheses of twelve substituted aryl ureas are given. Some of the other compounds of interest are: p-aminobenzaldehyde, N-bromoacetamide, o-chlorophenylthiourea, β-dimethylaminoethyl chloride hydrochloride, 3,5-dimethylpyrazole, ethyl pyruvate, laurone, α-phenylallylsuccinic acid and 2-thiophenecarboxaldehyde. The preparation of the last compound is an improved method of that given in Volume 29 of *Organic Syntheses*.

This volume contains the cumulative index to volumes 30 and 31.

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